REMARKS

Claims 1, 3, 8-22, 26, 27, 29, 30, 34-38, 40, 44-51 and 54-67 are pending. Claims 9, 14, 21, 27, 38, 47, and 54-65 are withdrawn from consideration. Claims 1, 11, 17, 26 and 34 have been amended. Claims 66 and 67 have been canceled without prejudice. No new matter has been added as a result of the amendments.

35 U.S.C. § 102(e) - Edmondson

Claims 1, 3, 34-35, 40 and 66-67 are rejected under 35 U.S.C. 102(e) as being anticipated by Edmondson et al. (US Patent 7,125,873).

> "Anticipation requires that the purported prior art reference disclose each and every limitation of the claim". *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

Applicant respectfully traverses the rejection of the instant claims on the grounds that Edmondson et al. does not teach each and every limitation of the instant claims.

Claim 1 and dependent claim 3 as newly amended, are drawn to a stabilized peptide formulation consisting essentially of the peptide PAP 66 or a salt thereof, a zinc salt, and a pharmaceutically acceptable organic solvent. Claim 34 and dependent claims 35 and 40, as newly amended are drawn to a stabilized dried mixture consisting essentially of a zinc salt and the peptide PAP 66 or a salt thereof.

Thus, the instant claims are drawn to a formulation or mixture containing essentially two components - - PACAP 66 and a zinc salt; and in the case of claims 1 and 3, these two components are present in a pharmaceutically acceptable organic solvent.

In contrast, Edmonson et al. teaches a pharmaceutical composition that comprises a compound of Formula I and at least one of PACAP, PACAP mimetics, and PACAP receptor 3 agonists, as illustrated below:

> "Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:
>
> > .....(i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists such as those disclosed in WO 01/23420", column 12, line 40 to column 13, line 4 of US 7,125,873.

The inclusion of a compound having Formula I in this composition taught by Edmonson et al. means that the cited composition is not encompassed by the formulation or mixture recited in the instant claims, as newly amended with essentially closed language. As described above, Applicant has amended claim 1 to recite a formulation consisting essentially of PACAP 66 or a salt thereof, a zinc salt, and a pharmaceutically acceptable organic solvent, and amended independent claim 34 to recite a mixture consisting essentially of a zinc salt and PAP 66 or a salt thereof. Neither claim, as amended provide for a composition containing Formula I, or other Formula disclosed by Edmonson et al.

Further, there is no specific teaching of PACAP 66 in Edmondson, as distinct from PACAP based materials. Thus, Edmondson et al. does not meet all the limitations of the instant claims which require the peptide PACAP 66, or a salt thereof.

Claims 66 and 67 are newly canceled by Applicant without prejudice, solely in the interest of advancing prosecution, rendering their rejection moot.

In light of the above remarks and claim amendments, Applicant respectfully requests reconsideration of the rejection of the instant claims.

35 U.S.C. § 103(a)- Claim 11

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Edmondson et al. (US Patent 7,125,873).

To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicant respectively traverses. Edmondson et al. does not teach all the limitations recited in the instant claims as newly amended, so the instant claims are not rendered obvious by Edmondson et al.

Claim 11 is drawn to a stabilized peptide formulation, either in a solution or in a suspension, consisting essentially of: (a) PACAP 66 (SEQ ID NO: 1) and/or salts thereof; (b) $ZnCl_2$; and (c) a pharmaceutically acceptable organic solvent.

The inclusion of a compound having Formula I in this composition taught by Edmonson et al. means that the cited composition is not encompassed by the formulation or mixture recited in the instant claims, as newly amended with essentially closed language. Thus, Claim 11, as amended does not provide for a composition containing Formula I, or other Formula disclosed by Edmonson et al.

Further, as discussed above, there is no specific teaching of PACAP 66 in Edmondson, as distinct from PACAP based materials. Thus, Edmondson et al. does not meet all the limitations of the instant claims which require the peptide PACAP 66, and/or a salt thereof.

Because the cited reference, Edmondson et al., does not teach all the limitations of the claims as newly amended, a prima facie obviousness has not been established as required by *In re Royka*.

In light of the above remarks and claim amendments, Applicant respectfully requests reconsideration of the rejection of claim 11.

35 U.S.C. § 103(a)- Claims 44-46 and 48-53

Claims 44-46 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oshaki et al. (US 5,428,129) in view of Thakur (US/2003 129133A1) and Edmondson et al. (US Patent 7,125,873)

Graham v. John Deere Co., 338 U.S. 1, 148 USPQ 459 (1966), recently reaffirmed by *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) provides the analytical framework for determining obviousness. Under *Graham*, obviousness is a question of law based on underlying factual inquires that address (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, and (3) the level of ordinary skill in the pertinent art. Evidence of secondary factors (e.g., commercial success, long-felt but unmet need, and unexpected results) are also given weight in the analysis. Moreover, to establish a prima facie obviousness rejection of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Predictability is required in maintaining a legal conclusion of obviousness under both *KSR* and the USPTO published guidelines.

Applicant respectfully traverses.

Independent claim 44 is drawn to a process for preparing a stabilized peptide formulation, comprising the steps of: (a) preparing an acid solution of acid and water; (b) cooling said acid solution to below room temperature; (c) mixing said cooled acid solution and the peptide PACAP 66 or a salt thereof to create a cooled mixture; and (d) drying said cooled mixture. Dependent claims 45-46 further limit the inorganic acid to HCl or H_3PO_4.

Dependent claim 49 further limits the ratio of the acid to PACAP 66 in the claimed method, dependent claim 50 further limits the drying step of the claimed method to freeze drying or spray

drying, and dependent claims 51-53 further add the additional step of adding a transition metal salt to said cooled mixture before drying said cooled mixture, where the transition metal includes zinc.

Thus, the claimed method comprises mixing the linear 31mer peptide PACAP 66 (SEQ ID NO:1) to a cooled aqueous acid solution, and drying the mixture, optionally in the presence of zinc.

In contrast, the primary reference used in the instant rejection (Ohsaki et al.) discloses processes for producing cyclic peptides.

The Office Action states that:

> "In 7 ml of TFA was dissolved 2.11 g of Boc-Ser(Bzl)-Asn-Leu-OPac under ice-cooling and the solution was allowed to stand at room temperature for 1 hour. The solution was then ice-cooled again and 2.5 ml of 4N HCl/dioxane was added. After shaking, the mixture was treated with diethyl ether and the resulting precipitate was collected by filtration and dried under reduced pressure over potassium hydroxide", column 27, lines 56-58.

The Office Action states on page 10 that Ohsaki et al.'s disclosure of mixing the peptide Boc-Ser(Bzl)-Asn-Leu-OPac with HCl/dioxane "meets the limitation of acid solution of acid and water". Applicant respectfully disagrees since the first step of independent claim 44 recites, in part, " preparing an acid solution of acid and water", which is cooled in a second step, and then followed with a later step of mixing the cooled acidic solution with PACAP 66. That is, the 31mer peptide PACAP 66 is added to the cooled acid solution. The acid solution recited in the instant claims contains only acid and water, with no mention of a third substance such as dioxane as cited in Ohsaki et al. In contrast, the Office Action cites Oshaki et al.'s teaching of in Column 27, above, of a cooled solution of HCl/Dioxane being added to the short peptide of Boc-Ser(Bzl)-Asn-Leu-OPac, not the complete 31mer elactonin (SEQID NO:1). Applicant contends that the cited method comprising the use of the peptide of Boc-Ser(Bzl)-Asn-Leu-OPac in Columns 27 and 28, is not comparable to the instantly claimed method using the 31mer peptide PACAP 66.

The Office Action further contends that the difference between the reference and the instant claims is that the reference does not teach PACAP 66 and transition metal salt.

To make up the difference, the Office Action cites Thakur's method of de novo synthesizing PACAP which includes the use of HCl in dioxane and Edmonson et al.'s teaching of a pharmaceutical composition comprising PACAP receptor.

Applicant notes that in contrast to the instantly claimed method for stabilizing PACAP 66, Thakur teaches a method of de novo synthesis of PACAP. Further, Thakur, does not teach PACAP 66. Similarly, Edmonson et al. does not teach PACAP 66, but a composition comprising both a compound with a specified formula (Formula I) and PACAP, as discussed above. Thus Applicant contends neither Thakur nor Edmondson combine to arrive at the claimed invention.

The Office Action premises its motivation to combine the references of Edmondson et al. and Thakur based on Ohsaki et al.'s teaching of a "method of preparing the stable peptide of a 31mer as well as other peptides", and that there is a reasonable expectation of success since Ohsaki et al. teach a 31mer peptide having the sequence of SNLSTXVLGKLSQELHKLQTYPRTDVGAGTP being prepared in such steps" page 11 of the Office Action. The Office Action refers to this sequence as SEQ ID NO:1. See page 9 of the Office Action.

However, Applicant notes that the 31mer taught by Ohsaki is described as a cyclic peptide, unlike the 31mer PACAP 66 peptide. See column 1, lines 20-30, of Ohsaki et al., as well as the sequence listing provided for the 31mer taught by Ohsaki et al. below.

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 31 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: both

(i i) MOLECULE TYPE: peptide

(i i i) HYPOTHETICAL: NO

(i v) ANTI-SENSE: NO

(i x) FEATURE:
(A) NAME/KEY: Cross-links
(B) LOCATION: join(1..6)
(D) OTHER INFORMATION: /note="L-aminosuberic acid forms a linkage between positions 1 and 6"

(i x) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 31
(D) OTHER INFORMATION: /note=carboxylamide

(x i) SEQUENCE DESCRIPTION: SEQ ID NO:1:

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Ser Asn Leu Ser Thr Xaa Val Leu Gly Lys Leu Ser Gln Glu Leu His
1               5                  10                  15

Lys Leu Gln Thr Tyr Pro Arg Thr Asp Val Gly Ala Gly Thr Pro
            20                  25                  30
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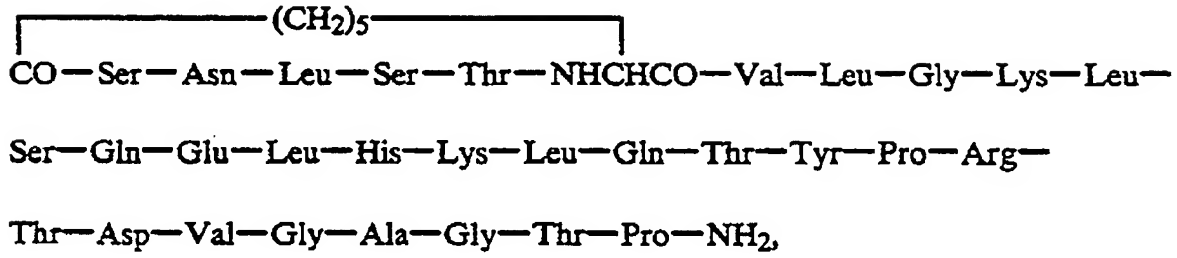

Applicant notes that the referenced method of de novo synthesis of a cyclic peptide does not provide one of skill at the time of the invention motivation or expectation of success for arriving at the claimed method of stabilizing PACAP 66, a linear peptide that has already been synthesized.

Further, given the cyclic nature of the referenced 31mer of SEQ ID NO:1, Applicant respectfully traverses the prediction of the Office Action on page 11 that "there is a reasonable expectation of success that the 31mer taught by Ohsaki and the 31mer PACAP 66 peptide "would at

least react the same way to process conditions", since the cyclic structure generally provides an increase in stability, and PACAP 66 is disclosed to be less stable than typical polypeptides.

Specifically, the instant specification teaches:

> "the degree of instability of PACAP 66 has, however, been found to be far greater than what is expected of a peptide in general", emphasis added, paragraph 0024 of the instant specification,
>
> and
>
> "surprisingly, the stability of this peptide in these organic solvents was as poor as, or even worse than, in an aqueous environment", paragraph 0006 of the instant specification.

Given the increased stability conferred to a peptide with a cyclic structure, such as one taught by Ohsaki et al. relative to a linear structure with the same number of amino acids, and given that the present specification teaches that the stability of PACAP 66 is less than that of other typical peptides, Applicant contends that one of skill could not have reliably predicted that "the 31mers would at least react the same way to the process conditions" taught by Ohsaki et al. in their method of preparing a stabilized peptide formulation, as asserted by the Office Action on page 11. In view of the atypical instability of the PACAP 66 peptide, Applicant contends that one of skill in the art at the time of the invention would not have had a reasonable expectation of success in developing a method of preparing a stable formulation of PACAP 66 at the time of the invention, based on the teachings of Ohsaki et al.

The Office Action justifies that one of skill would have had a reasonable expectation of success on the grounds that the Supreme Court has upheld the "obvious to try" test as an appropriate test under 35 U.S.C. 103. However, as discussed above, predictability is required in maintaining a legal conclusion of obviousness under both *KSR* and the USPTO published guidelines. The Office Action provides no grounds on which one of skill could predictably arriving at the claimed invention.

Applicant contends that in view of the instability of PACAP 66 peptide and in view of the generic teachings of Edmondson regarding pharmaceutical compositions, the combination of references does not render the instant claims obvious. Instead, the cited combination of references provides a hindsight reconstruction of the claimed invention based on the instant specification, which is not permissible.

In light of the above remarks and claim amendments, reconsideration and withdrawal of the rejection is respectfully requested.

35 U.S.C. § 103(a)- Claims 1, 3, 8, 10-13, 15-20, 22, 26, 29-30, 34-37, 40 and 66-67

Claims 1, 3, 8, 10-13, 15-20, 22, 26, 29-30, 34-37, 40 and 66-67are rejected under 35 U.S.C. 103(a) as being unpatentable over Edmondson et al. (US 7,125,873) in view of Pallenberg et al. (US Patent No. 5,538,945) and Maccecchini (U.S. Patent 5,830,998) and Bolin (US 5,234,907) and Igari et al. (US 2002/0058622A1).

Applicant respectfully traverses on the ground that the primary reference, Edmondson et al., does not teach all the limitations recited in the instant claims as newly amended.

As described above, Applicant has amended claim 1 to recite a formulation consisting essentially of PACAP 66 or a salt thereof, a zinc salt, and a pharmaceutically acceptable organic solvent, and amended independent claim 11 to recite a peptide formulation consisting essentially of PACAP 66 and/or salts thereof, $ZnCl_2$, and a pharmaceutically acceptable organic solvent, and amended independent claim 17 to recite a stabilized peptide formulation, consisting essentially of a dried mixture of an acid, the peptide PACAP 66 or a salt thereof, and a zinc salt, and amended independent claim 26 to recite a stabilized peptide formulation, consisting essentially of a dried mixture of an inorganic acid, PACAP 66 and/or a salt thereof, and a zinc salt, and amended independent claim 34 to recite a mixture consisting essentially of a zinc salt and PAP 66 or a salt thereof.

As illustrated below, the composition taught by Edmondson et al. does not consist essentially of PACAP:

> "Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be administered in combination with a compound of Formula I, and either administered separately or in the same pharmaceutical composition, include, but are not limited to:
>
> > .....(i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists such as those disclosed in WO 01/23420", column 12, line 40 to column 13, line 4 of US 7,125,873,

As discussed above, Edmondson's inclusion of a compound having Formula I in the results in the cited composition not being encompassed by the formulation or mixture recited in the instant claims, as newly amended with essentially closed language. Thus, the instant claims, as amended does not provide for a composition containing Formula I, or other Formula disclosed by Edmonson et al.

Further, as discussed above, there is no specific teaching of PACAP 66 in Edmondson, as distinct from PACAP based materials. Thus, Edmondson et al. does not meet the limitation of the instant claims which require the peptide PACAP 66, and/or a salt thereof.

Therefore, the instant claims, as amended, do not provide for a composition containing Formula I, or other Formula disclosed by Edmonson et al, in addition to PACAP 66. Applicant has canceled claims 66-67, without prejudice, rendering their rejection moot.

Pallenberg's teaching that peptide-copper complexes formulated for administration may contain DMSO, Maccecchini's teaching of a peptide formulation comprising an organic solvent and a transition metal, Bolin's teaching of organic solvents, TFA, HCl and lyophilization, and Igari's teaching of a water insoluble, polyvalent metal salt of a water soluble substrate, do not make up for Edmondson et al.'s not teaching a formulation consisting essentially of PACAP 66. Thus Applicant contends that the referenced teachings, when taken individually or in combination, do not arrive at the claimed invention

The Office Action states that the difference between the primary reference (Edmondson) and the instant claims is that the reference does not teach DMSO as the organic solvent, the claimed molar ratio, the concentration of PACAP 66, and the inorganic acid.

The Office Action states that one of skill would have been motivated to add in DMSO since DMSO is a penetration enhancement agent used in topical and injection formulations. Page 16 of the Office Action.

The Office Action states that one of skill would have been motivated to use $ZnCl_2$, since it is a pharmaceutically acceptable salt that is used in pharmaceutical compositions that are in an injectable or oleaginous suspension.

However, the Office Action fails to provide a motivation to support the contention that it would have been obvious to one of skill in the art to combine the teachings of Edmondson et al., Pallenberg et al., Macchecchini et al., Bolin and Igari to formulate a stabilized peptide formulation in DMSO and $ZnCl_2$ salt, as stated on page 16 of the Office Action. The Office Action asserts that there was a reasonable expectation of success since zinc salts are readily available, and a pharmaceutically acceptable salt, and since DMSO is safe for topical administration and injection, see page 17 of the Office Action.

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)

The cited references do not anywhere suggest Applicant's PACAP 66 formulations. Further, given the sheer number of references used to construct the obviousness rejection, Applicant respectfully submits that the rejection is based on impermissible hindsight, using Applicant's specification as a blueprint. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. See MPEP 2142.

Further, Applicant respectfully disagrees with the assertion by the Office Action that there was a reasonable expectation of success based on the referenced teachings. The lack of a reasonable

expectation of success in achieving the claimed stabilized formulation is evidenced by Applicant's efforts to creatively develop an unexpectedly satisfactory solution to arrive at the claimed stabilized peptide formulation.

Thus, as disclosed in the specification, Applicant surprisingly found that addition of the metal salt zinc chloride in an organic solvent turned out to be very effective in stabilizing the peptide. The specification further discloses that "the stabilization of PACAP 66 in an organic solvent by zinc salt was surprising, because several metal salts failed to stabilize PACAP 66 in an aqueous solution. (See, e.g., FIG. 1)", and that "these stabilization strategies were also found to be effective in organic solvent-based suspensions and in a dried state during storage".

In addition to the unpredictability in achieving a stable formulation of PACAP 66 described above, nonobviousness of the instantly claimed formulation is buttressed by the specification's disclosure that Applicant was the first to provide a stable formulation of PACAP 66 using $ZnCl_2$ in an organic solvent:

> "For the first time, we demonstrated that $ZnCl_2$ can be used as a formulation excipient to stabilize a peptide in an organic solvent, in an organic solvent-based suspension, or in a dried state", emphasis added, paragraph 0045 of the instant specification.

In view of the unpredictability in achieving PACAP 66 stabilization in DMSO using $ZnCl_2$, Applicant contends that one of skill at the time the invention was made would not have had a reasonable expectation of success based on inclusion of zinc in the laundry list of pharmaceutically acceptable salts disclosed by Edmonson et al. That is, the skilled artisan would not have been able to predict that the claimed formulation specifically, would have been effective in increasing the stability of this uncharacteristically unstable protein PACAP 66. As discussed above, the present specification teaches that the stability of PACAP 66 is less than that of other typical peptides, and further, that PACAP 66 is not stable in an aqueous environment containing zinc salts.

In view of the PACAP 66's unusual instability, Applicant contends that one of skill at the time the invention was made would not have had a reasonable expectation of success reconstructing

Applicant's stable formulation of PACAP 66 based on picking and choosing each of the recited components of the instantly claimed formulation; i.e., the peptide component, the metal salt component and the organic solvent component, from components taught in the cited references, none of which addressed the problems associated with stabilizing formulations of unstable proteins.

That is, none of the references state anything regarding the differential stability of the instantly recited peptide PACAP 66 in a formulation comprising a zinc salt, compared to another salt such as aluminum, etc., nor in a formulation comprising an aqueous solvent compared to an organic solvent. For example, Pallenberg et al.'s teaching of peptide-copper complexes (not zinc), which may be formulated to contain DMSO does not provide the missing limitation in Edmonson with respect to providing the instantly recited stabilized peptide formulation of the peptide PACAP 66 or a salt thereof, a zinc salt, and a pharmaceutically acceptable organic solvent. Although each of the references separately mentions each component of the instantly claimed formulation, they do not teach or provide the motivation for the composite, formulation in which PACAP 66 is stable, since they do not address the issue of formulations of unstable proteins. In view of the instability of PACAP 66, Applicant contends that the recited limitations of the instant dependent claims, e.g., $ZnCl_2$:peptide molar ratio and PACAP 66 concentrations, are not predictable and thus are not obvious.

In light of these remarks and claim amendments, Applicant respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

In view of the amendments and arguments presented above, Applicants believe the pending application is in condition for allowance. Should the Examiner believe that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, she is cordially invited to call the undersigned attorney/agent. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Date: 2/6/09

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